Case Report

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Unveiling the Mystery of Thanatophoric Dysplasia: A Case Report on Clinical and Radiological Correlation in a Low-Antenatal Care Setting

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ABSTRACT

Thanatophoric Dysplasia (TD) is a rare, lethal skeletal dysplasia caused by FGFR3 gene mutations, leading to severe bone and cartilage abnormalities. TD is classified into two subtypes: Type 1, characterized by bowed femurs and a normal skull, and Type 2, with straight femurs and a cloverleaf skull deformity. Common features include micromelia, macrocephaly, a narrow thorax, and respiratory insufficiency. We report a case of 32-year-old primigravida presented at 28 weeks gestation with reduced fetal movements and no prior antenatal visits. Ultrasound revealed breech presentation, limb shortening, and macrocephaly. Labor was induced, resulting in a preterm vaginal delivery. Postnatal examination showed bowed femurs, short ribs, and a narrow thorax. Despite intensive care, the infant developed respiratory distress and died on the fourth day. Radiological findings, including macrocephaly and telephone receiver deformity of the femurs, confirmed Type 1 TD.

Keywords: Thanatophoric Dysplasia, Macrocephaly, Craniosynostosis, Chorioamnionitis, Achondroplasia.

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Introduction

Osteochondrodysplasia refers to a group of heterogenous hereditary disorders characterized by abnormality in development of bone and cartilage. Out of these, Thanatophoric dysplasia is a rare and highly fatal congenital disorder caused by a de novo mutation in the extracellular region of the fibroblast growth factor receptor 3 (FGFR3).[1] Its prevalence evaluated in Japan is about 1.1 (95%CI: 0.84–1.37) per 100,000 births.[2] Thanatophoric dysplasia (TD) is generally acknowledged at birth by features such as short limbs (micromelia), a small conical chest, flat vertebral bodies (platyspondyly), and an enlarged head (macrocephaly) and is further categorized into two subtypes, Type I and Type II, which share overlapping features but are distinguished by skull and femur morphology. Type I typically presents with micromelia and bowed femurs, sometimes along with craniosynostosis of different intensity. In comparison, Type II consists of micromelia with straight femurs and frequently presents with moderate to severe craniosynostosis, often resulting in cloverleaf like skull deformity.[3] This condition can be diagnosed as early as 13 weeks of gestation by antenatal screening.[4] Fetal death is generally because of severe respiratory insufficiency due to reduced thoracic capacity and underdeveloped lungs, or respiratory failure due to compression of brainstem.[3]

This case report documents, a 32 year old primigravida who presented at 28 weeks of gestation with complaint of reduced fetal movements. Upon examining the patient the symphysio fundal height corresponded to 28 weeks of gestation; however, the ultrasound showed a femur length corresponding with 17 weeks of gestation, while the biparietal diameter (BPD) and head circumference coinciding to 28 weeks. Preterm labor was induced due to oligohydramnios. Based on the radiological and morphological findings below, a Thanatophoric dysplasia

Type I diagnosis was established. We report this case due to the rarity of this congenital disorder in Pakistan.

Methodology

A 32-year-old primigravida, presented to POF Hospital Wah Cantt at 28 weeks of gestation with concerns about reduced fetal movements over the past week. She was not previously registered for antenatal care and had no prior examinations or investigations for her current pregnancy. Her medical history was unremarkable, with no hypertension, diabetes, hepatitis, or other illnesses. She did not smoke or consume alcohol. Investigations revealed leukocytosis and elevated CRP levels, while hepatitis and syphilis serology were negative. Her renal and liver function tests were normal. Examination showed a symphysis fundal height of 28 weeks. Ultrasound indicated a single live fetus in breech presentation, with a femur length of 24mm corresponding to 17 weeks, a BPD of 70mm corresponding to 28 weeks, and a head circumference of 265mm. The fetus was small based on biophysical parameters and abdominal circumference. The parents were informed about the seriousness of the case.

Her labor was induced due to significantly reduced amniotic fluid and the risk of chorioamnionitis. The baby was in a breech lie and was delivered preterm via spontaneous vaginal delivery. The baby was cyanosed at birth. Vitamin K was administered immediately. The APGAR score was 4/10 at one minute and 5/10 at five minutes. Despite continuous stimulation and suctioning efforts, the baby did not cry. The pediatric team performed ambu bagging for resuscitation, as the baby exhibited symptoms of respiratory distress syndrome (RDS). The baby was admitted to the NICU for further evaluation. Injection surfactant and ventilatory support via B-CPAP were provided. Unfortunately, despite these efforts, the baby passed away four days after birth.

Examination of the baby revealed a birth weight of 1.9 kg. Head size was normal. There was frontal bossing. The baby had a short neck, a low set of ears, and a slightly depressed nasal bridge. The baby had a short thoracic circumference and a wide-open anterior fontanelle. There were multiple folds on limbs, bowed lower limbs, and rhizomelia as shown in Figure 1. The genital examination revealed normal testis.

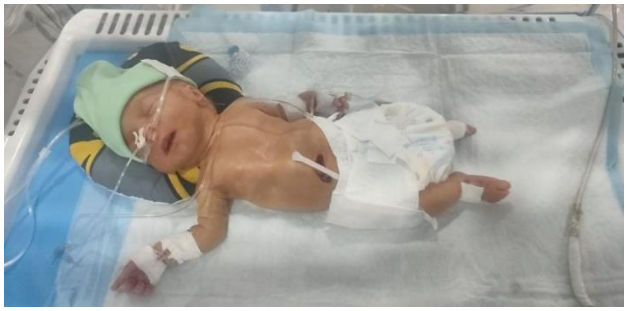

Figure 1. Infant with short neck, low set of ears, and short thoracic circumference characteristic of Thanatophoric dysplasia/

X-ray chest and infantogram were ordered for further evaluation, revealing macrocephaly, short thick tubular bones of extremities, bowing of shaft of femur characteristics of telephone receiver deformity as shown in figure 2.

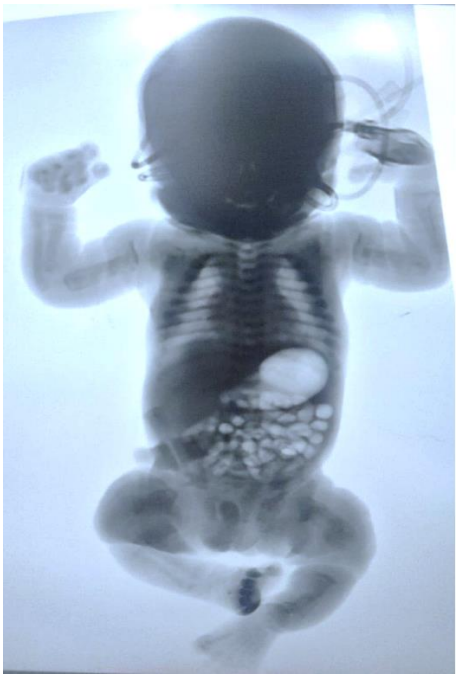

Figure 2. Infantogram of infant with Typical Thanatophoric Dysplasia type 1

X-ray lumbar spine lateral view revealed that vertebral bodies, spinous processes, pedicles, and transverse processes are normal with no fracture or bony deformity seen. Based upon these radiological and morphological features diagnosis of Thanatophoric dysplasia type 1 was made.

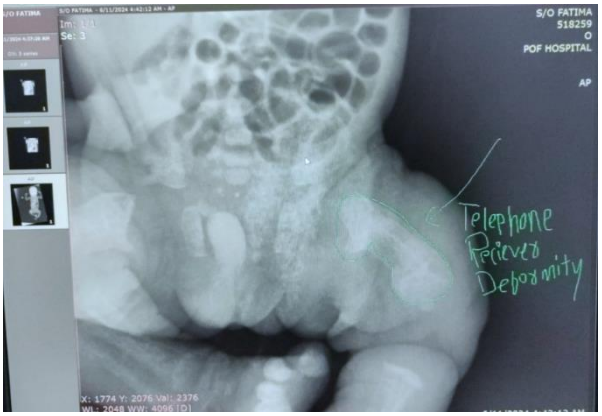

Figure 3. Showing an X-ray of the baby with telephone receiver deformity of the femur

Discussion

Thanatophoric dysplasia (TD), a severe skeletal dysplasia, is virtually always lethal neonatally.[5] The term is derived from the Greek words "Thanos", meaning death, and "Phoros", meaning bringing, reflecting its fatal nature. This disorder was classified into the osteochondrodysplasias group at First International Conference on the Nomenclature of Skeletal Dysplasia in 1969.

Thanatophoric dysplasia has two types differentiated based on radiological characteristics mainly that type 1 is a more common subtype with normal skull and bowed femurs like telephone receivers (hence called telephone receiver deformity). In contrast, type 2 has straight femurs and a cloverleaf skull. Features common to both subtypes include micromelia, short ribs, narrow thorax, brachydactyly, redundant skin folds along the limbs, distinctive facial features, and relative macrocephaly. Our patient had all the common features revealed by an infantogram and characteristic bowed lower limbs indicating type 1 Thanatophoric dysplasia.

The patient's radiological and clinical findings, including characteristic bone abnormalities, strongly suggested the diagnosis. Early detection of skeletal dysplasias is possible, with ultrasound identifying key features as early as 13 weeks of gestation.[4] and identification of TD can be done in 2nd trimester by ultrasound hence, specific diagnosis requires a three-dimensional ultrasound. Since our patient had no history of antenatal checkup the initial diagnosis was only made on ultrasound done when the patient presented at 28 weeks with reduced fetal movements and leaking amniotic fluid. Genetic analysis could not be conducted due to lack of facilities. Final diagnosis our case was made on birth.

Mutations in the fibroblast growth factor receptor 3 (FGFR3) gene were identified in both subtype and prenatal diagnosis is done by molecular analysis of FGFR3 gene extracted from fetal cells obtained by amniocentesis at 15-18 weeks gestation or by chorionic villous sampling performed at 10-12 weeks gestation.[6] However, this was not performed in our case because there is no family history of TD and most fetuses die in utero those who survive are dependent on a ventilator, hence it is not passed onto the next generation. A nationwide survey in Japan concluded that out of the 51 live newborns, 27 died ≤7 days after birth, with an early neonatal mortality rate of 56% [2] This aligns with our patient who died within four days of birth due to respiratory distress syndrome. The survey also noted short limbs in all patients as well as; narrow thorax in 90%; respiratory insufficiency in 84%; and bowed femurs in 78%, all three findings were present in our case.

Prediction of lethality is important for management and discussion of termination. It can be determined using chest size, a few reports also suggest that a femur length/AC ratio <0.16 is a sensitive threshold for predicting lethal skeletal dysplasia.[7] A study of prenatal diagnosis of TD corroborated this by evaluating 35 cases in the study and all TD cases reported in the literature that included the femur length/AC ratio, had an FL/AC ratio of <0.16. [8] This also coincides with our case as the FL/AC ratio was 0.11 indicating severe lethality.

In cases of Thanatophoric Dysplasia (TD), cesarean delivery is often preferred. A Japanese study reported that among 31 live births with documented delivery methods, 12 were cesarean sections. The primary reasons included cephalopelvic disproportion, breech presentation, and maternal preference for surgical delivery whereas in our case the fetus was born via induced vaginal delivery despite breech presentation as mother presented with premature labor. [2] In our case, no maternal complications were reported which is a rarity as most pregnancies with Thanatophoric dysplasia are frequently complicated by hydramnios, prematurity, and cephalopelvic disproportion.

Our case had no family history of TD which is also mentioned in literature including a study of achondroplasia and TD in the United States where none of the reported 48 cases of TD were inherited, but the study also showed that in Texas, fathers greater than 40 years of age had significantly increased rates of de novo achondroplasia among their offspring compared with younger fathers. An advanced paternal age effect was

reinforced by a case report from Hong Kong where the father was 48 years old.[9] Advanced age was also a risk factor in our case as the father's age was 42 years. Maternal age and birth order are not related to this condition.[10]

A postnatal autopsy of the affected fetus to confirm the diagnosis by histopathology could not be performed in our case as consent was not given by the parents. Very few cases have been reported in Pakistan to date. Differential diagnosis of TD includes achondroplasia and hypochondroplasia as these two conditions also have FGR3 mutations and thus radiological differences and clinical characteristics are needed for correct diagnosis.

Conclusion

This case underscores the lethal nature of Thanatophoric Dysplasia (TD) and the critical role of early prenatal screening, especially in low-resource settings. The diagnosis, confirmed by classic radiological features (micromelia, macrocephaly, and "telephone receiver" femurs), was delayed due to lack of antenatal care. Despite intervention, respiratory failure led to neonatal death, highlighting TD's poor prognosis. Advanced paternal age may be a risk factor. Improved access to prenatal ultrasound and genetic counseling is essential for timely diagnosis and family guidance.

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